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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/331,376	06/18/99	FODSTAD	0 7885.65USWO

EXAMINER	
DAVIS, M	
ART UNIT	PAPER NUMBER
1642	16

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DATE MAILED: 04/11/00

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1-10-00.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-4, 6-11, 13-14 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-4, 6-11, 13-14 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

* U.S. GPO 1996-409-290 40029

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence

Applicant's election with traverse of species antibodies, and tumor associated antigens in Paper No. 8 is acknowledged. The traversal is on the ground(s) that applicant does not wish to be constrained to the Examiner's rationale. This is not found persuasive because the searches for patentably distinct species are not co-extensive, and thus it would be a burden for the Examiner to search all of the species together.

The requirement is still deemed proper and is therefore made FINAL.

Applicant cancels claims 5 and 12.

Accordingly, claims 1-4, 6-11, 13-14, species antibodies, and tumor associated antigens are examined in the instant application.

OBJECTION

1. Claim 14 is objected to, because it seems that the sizes of the particles, "0.01μm-6μm" are mispelled as "0.01Tm-6Tm". Similarly, it seems that " 0^0C to 25^0C" is mispelled as "00C to 250C".

2. The language of claim 1, from "each antibody....through .....ranges from 20:1 to 0.5:1" is obscure and complex. Correction is required to clarify the claim.

PRIORITY DATE

The Examiner has established as a priority date 06/18/99 for the instantly claimed application serial number 09/331376, because the application to which priority is claimed does not recite the limitation "except when the target cells are malignant and normal haematopoietic and lymphatic cells".

If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of 06/18/99 for the instantly claimed application serial number 09/331376, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

REJECTION UNDER 35 USC 101

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 9-11, 13 are rejected under 35 U.S.C. § 101 because they are drawn to non statutory subject matter. The claim reads "Use of the method to detect and phenotype target cells of claim 1". "Use of a method" is not a statutory class of invention under 35 U.S.C. § 101.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 1-4, 6-11, 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1-4, 6-11, 13-14 indefinite because claims 1 and 14 recite the language "each antibody conjugated to each of several types of particles". Claims 1 and 14 are confusing because it is not known whether each antibody is conjugated to several types of particles, or each antibody is conjugated to one type of particles.

2. Claims 1-4, 6-11, 13-14 are indefinite because claims 1 and 14 recite the language "0.01 μm- 6 μm". Is this drawn to the sizes of the antibody conjugate or the particle alone.

3. Claims 1-4, 6-11, 13-14 indefinite because claims 1-4, 6-8, 14 recite the language "characterized". It is unclear whether the term is drawn to the method or the antibodies. This rejection could be obviated by amending the claims to substitute "characterized" with the term "wherein".

4. Claims 1-4, 6-11, 13-14 indefinite because claims 1 and 14 recite the language "such as", which does not set forth the metes and bounds of the patent protection desired.

5. Claims 1-4, 6-11, 13-14 indefinite because claims 1 and 14 recite the language "a per se known enrichment procedure". It is not clear what type of "per se enrichment" is.

6. Claim 6 is indefinite for the use of the language 'listed in Table 1". The rejection could be obviated by reciting a Markush group including the antigens of table 1.

7. Claims 6, and 7 are indefinite because claim 7 is dependent on claim 1, which specifically recites that the method is not used with malignant cells.

8. Claim 13 is indefinite because there is no antecedent basis in claim 1 for the adhesion molecules, the growth factor, the carcinoma markers, the carbohydrate antigens, the melanoma antigens, the sarcoma antigens, the glioma antigens, the motility associated markers, the proliferation associated antigens, the differentiation associated markers, the

drug resistance markers, the angiogenesis associated antigens, the invasion related markers, and the other antigens.

9. Claim 13 is indefinite for the recitation of the language apoptosis "associated" markers, motility "related' markers, proliferation "associated" antigens, differentiation "associated" markers, invasion "related" markers, and the "other' antigens. It is not clear what kind of association or relation said markers or antigens have with apoptosis, motility, proliferation, or invasion. It is not clear what type of invasion is claimed. It is not clear the "other" antigens are other to what antigens.

10. Claims 1-4, 6-11, 13-14 indefinite because claims 1 and 14 recite the language "the number or of particles". Does applicant mean "the number of particles"?

11. Claim 14 is indefinite, because it is dependent on canceled claim 5.

12. Claims 9-11, and 13 are confusing for the recitation of the term "Use" of a method.

13. For the clarity of the claims, the following language is suggested for the the language "2-6",. "from 0.01μm-6μm", and "5-10 minutes to 2 hours" of claim 1, and "from 0.5μm-4.5μm" of claim 2: "2 to 6", "from about 0.01μm to about 6μm", " about 5 minutes to about 2 hours", and "from about 0.5μm to about 4.5μm".

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, LACK OF ANTECEDENCE

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o).

Claims 1, and 14 are drawn to a kit and a method to detect and phenotype target cells, by using several types of particles coated with antibodies, wherein each antibody is conjugated to each of several types of particles. Claims 1 and 14 read on a kit and a

method to detect and phenotype target cells, by using several types of particles coated with antibodies, wherein each one antibody is conjugated to several types of particles.

The specification however does not disclose a method to detect and phenotype target cells, by using particles coated with antibodies, wherein each one antibody is conjugated to several types of particles.

2. Claims 1 and 14 are drawn to a kit and a method to detect and phenotype target cells, except when the target cells are malignant and normal heamotopoietic and lymphatic cells.

The specification however only discloses a method for indentifying and characterize pathological cells. The specification does not disclose a kit and a method to detect and phenotype target cells, except when the target cells are malignant and normal heamotopoietic and lymphatic cells.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims 1-4, 6-11, 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a kit and a method to detect and phenotype target cells, by using several types of particles coated with antibodies, wherein each antibody is conjugated to one separate type of particles, does not reasonably provide enablement for a kit and a method to detect and phenotype target cells, by using several types of particles coated with antibodies, wherein each antibody is conjugated to each of several types of particles. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 1-4, 6-11, 13-14 are drawn to a kit and a method to detect and phenotype target cells, by using several types of particles coated with antibodies, wherein each

antibody is conjugated to each of several types of particles. Claims 1-4, 6-11, 13-14 read on a kit and a method to detect and phenotype target cells, by using several types of particles coated with antibodies, wherein each antibody is conjugated to several types of particles. The specification discloses that four types of microspheres directed to four different antigenic determinants are conjugated to four different antibodies (p.5), and that different types of particles could be separated by fluorescence, color and sizes. The specification however does not disclose a kit and a method to detect and phenotype target cells, by using several types of particles coated with antibodies, wherein each antibody is conjugated to several types of particles. The specification does not disclose how to use the claimed method to screen target cells, wherein each antibody is conjugated to several types of particles. The specification does not disclose how to make coated particles for use in the claimed method to screen target cells, wherein each antibody is conjugated to several types of particles. The specification does not disclose where on the antibody to conjugate several particles which are much larger than the antibody by itself, wherein said particles would not interfere with the conformation and binding of said antibody. It is unpredictable that each antibody conjugated to several particles, could still retain its binding property and function, because it is well known in the art that altering the shape of an antibody by structural interference would alter the binding and function of an antibody. The specification provides insufficient guidance with regards to these issues. The specification fails to provide an enabling disclosure for a kit and a method to detect and phenotype target cells, by using several types of particles coated with antibodies, wherein each antibody is conjugated to several types of particles. One of skill in the art would not know how to make the coated particles, and use the claimed method, because different cells could not be sorted according to the characteristic or property of the particles, which are bound to the cells via the specific antibodies, and because the specification does not disclose how to make particles coated with antibodies, wherein each antibody is

conjugated to several types of particles. Therefore, undue experimentation would be required to practice the claimed invention.

2. Claims 1-4, 6-11, 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to detect and phenotype malignant cells, does not reasonably provide enablement for a method to detect and phenotype any target cells, except malignant and normal haematopoietic and lymphatic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Claims 1-4, 6-11, 13-14 are drawn to a method to detect and phenotype target cells, except malignant and normal haematopoietic and lymphatic cells, by using particles coated with antibodies, which are directed against antigenic determinant on the target cells. The specification discloses a method to detect and phenotype target tumor cells, by using particles coated with antibodies, which are directed against antigenic determinant on the target tumor cells. The specification, however, does not disclose a method to detect and phenotype any target cells, except malignant and normal haematopoietic and lymphatic cells. The specification does not disclose specific antigens, nor corresponding antibodies, for any target cells, except except malignant and normal haematopoietic and lymphatic cells. Without the teaching of specific antibodies used for coating the particles, it is unpredictable that the target cells could be detected and phenotyped, because the particles which are coated with antibodies are not specifically directed to any target cells. Thus one cannot extrapolate the teaching of the specification to the scope of the claims.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly claimed.

Furthermore, claim 7 is inoperative for the following reasons: Claim 7 is drawn to a method of detecting target cells, wherein the particles used for the method are coated

with antibodies directed to tumor associated antigens. Claim 7 however is dependent on claim 1, which specifically recites that the method is not used with malignant cells.

REJECTION UNDER 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-4, 6-11, 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hajek et al, 1994, PN=5,340,719, in view of Fostad et al, 1994,. WO 94/07139, and O'briant KC et al, 1991, Cancer, 68: 1272-1278.

Claims 1-4, 6-11, 13-14 are drawn to a kit and a method to detect and phenotype target cells, except when the target cells are malignant and normal heamotopoietic and lymphatic cells. Said method comprises using several types of particles, which are coated with 2-6 antibodies directed against antigenic determinants expressed on target cells, wherein each antibody is conjugated to each of several types of particles. Said particles are instrumentally or visually separable by fluorescence, color and size, with sizes ranging from about 0.01μm to about 6μm, or from about 0.5μm to about 4.5μm, wherein the ratio between the number of particles and the number of cells ranges from 20:1 to 0.5:1. Said antigenic determinants are tumor associated antigens, as recited in claims 8 and 13. Said antibody-coated particles are incubated, under gentle rotation for about 5 minutes to 2 hours, with cell suspension containing target cells at 0^0C to 25^0C. The resulted target cell rosettes are evaluated microscopically and/or by suitable visualizing or imaging devices.

For the interest of compact prosecution, claims 1-4, 6-11, 13-14 are interpreted as being drawn to a kit and a method to detect and phenotype target tumor cells. Said method comprises using several types of particles, which are coated with 2-6 antibodies directed against antigenic determinants expressed on target cells, wherein each antibody is conjugated to a separate type of particles.

Hajek et al teach an optical screening method for identifying both the morphology and selected characteristics or properties expressed by whole blood or bone marrow cells. Said method could be used for cancer or other abnormal cells from tissues or from blood samples (column 3). The cells are combined with a plurality of sets of microspheres, each

set having a reactant bound specifically to a different specific molecule on at least one type of cell (claim 18). Hajeck et al defines that a reactant could be an antibody, and a specific molecule could be an antigen (column 3). Hajek et al teach that the microspheres are of 0.7, 1.3. 1.05, 2.17 and 3.06 micron diameter (column 8). In other words, the sizes of the microsphere taught by Hajek et al overlap with those in the claimed method. Hajek et al also teach that the different sets of microsphere are optically differentiated by having different optical characteristics, such as size, shape, color, or combination thereof (abstract). Hajek et al further teach that lymphocyte subsets now conventionally are determined by fluorescent labeling of the cells, with fluorescent-tagged antibodies. The samples are analyzed by a fluorescent microscope, or by flow cytometry instrument (column 2).

Although Hajek et al teach that the suggested ratio of bead volume and whole blood is about 10 ul of 1% solution of 2.17 micron microspheres per about 20,000 white blood cells (column 9), Hajek et al do not teach that the ratio between the number of microspheres and the number of cells ranges from 20:1 to 0.5:1. Hajek et al do not teach the tumor associated antigens recited in the claims 8 and 13 of the instant application. Hajek et al do not teach that antibody-coated particles are incubated, under gentle rotation for 5-10 minutes to 2 hours, with cell suspension containing target cells at 0^0C to 25^0C.

Fostad et al teach a method of detecting specific target tumor cells, by coating paramagnetic particles or beads with antibodies against membrane structures specifically expressed on target cells. Said antibody-coated particles are incubated with target cells for 5-10 min to 2 h, preferably 30 min, at a temperature between 0^0C to 25^0C, under gentle rotation. In other words, the incubation condition taught by Fostad et al is the same as the claimed incubation condition (p.7). Fostad et al further teach that the number of antibody-coated beads added to the cell suspension should be 1-10% of the total number of cells, if the number of target cells is unknown (p.8). The ratio of 1-10% taught by Fostad et al is

within the range from 20:1 to 0.5:1 in the claimed method. Fostad et al also list relevant tumor antigens, and associated antigen-binding antibodies for use in detecting target tumor cells (table 1). Said tumor associated antigens are similar to those recited in the claims 8 and 13 of the instant application.

O'Briant et al teach that breast cancer cells within tumors and within cell lines vary markedly with regard to their antigenic phenotype. Use of multiple monoclonal antibodies can compensate for this heterogeneity observed within and between tumors (p.1276).

The art establishes that it was possible at the time the invention was made to screen target whole blood or bone marrow cells using a plurality set of microspheres, each set having a reactant bound specifically to a different specific molecule on at least one type of cell (claim 18). The different sets of microsphere are optically differentiated by having different optical characteristics, such as size, shape, color, or combination thereof. The art further teaches that said method could be applied for screening target tumor cells. The art also teaches specific conditions for incubating antibody-coated particles with tumor cells, such as the duration of incubation, temperature, and the ratio of particles and tumor cells. In addition, the art teaches relevant tumor antigens which could be targeted by available antibodies.

Therefore, it would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to screen tumor cells using a plurality set of microspheres, each set having a reactant, or an antibody, bound specifically to a different specific molecule, or an antigen, on at least one type of cell, wherein the different sets of microsphere are optically differentiated by having different optical characteristics, such as size, shape, color, or combination thereof, as taught by Hajek et al. It would have been obvious to a person of ordinary skill in the art to use the method taught by Hajek et al to screen tumor cells because of the following reasons: 1) Hajek et al teach that said method of screening target cells using a a plurality set of microspheres, each set coated with a

different antibody, could be applied to screen tumor cells as well, and 2) there is a heterogeneity of antigenic phenotype within tumors, and even within tumor cell lines, such as in breast cancer cells, as taught by O'Briant et al. It would have been obvious to use conditions for incubating antibody-coated particles with tumor cells, such as the duration of incubation, temperature, the ratio of particles and tumor cells, and relevant tumor antigens which could be targeted by available antibodies, as taught by Fostad et al, because said parameters are optimal for tumor cells. One of ordinary skill in the art would have been motivated to screen target tumor cells using a a plurality set of microspheres, each set coated with a different anti-tumor antibody, with a reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 10:00 am to 2:00 pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor,Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

March 20, 2000

SUSAN UNGAR
PATENT EXAMINER